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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/727,030	11/30/2000	Patrick N. Gilles	612,404-370	3744

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EXAMINER	
KIM, YOUNG J	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 05/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/727,030	GILLES ET AL.	
	Examiner	Art Unit	
	Young J. Kim	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21* is/are rejected.

7)☒ Claim(s) *1 and 10* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 November 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/28/01, 3/26/01, 1/26/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The Group and/or Art Unit location of your application in the PTO has been assigned to Art Unit 1637. All further correspondence regarding this application should be directed to Group Art Unit 1637.

Priority

Applicants' priority claim under 35 U.S.C. 120 to PCT/US00/08617 and under 119(e) to 60/126,85 is acknowledged.

Information Disclosure Statement

The Office acknowledges the IDS received on February 28, 2001, March 26, 2001, and January 26, 2004.

With regard to IDS's received on February 28, 2001 and January 26, 2004, Applicants state that in accordance with 37 CFR 1.98(d), copies of some or all of the references listed on the PTO-1449 have not been provided because, "they were previously cited by or submitted to the Patent and Trademark Office in prior Applications for which a claim for priority under 35 U.S.C. 120 has been made." Applicants are reminded that the application for which priority claim under 35 U.S.C. 120 is made is a PCT application, the application of which had no previously filed IDS nor references. The three references cited in the corresponding International Search Report (ISA/210) have been considered, however as they were cited by the Examiner of record. Therefore, while the U.S. Patents cited therein have been considered, the remainder of the references, especially the non-patent literatures, **have not been** considered as none of the references have been provided in the instant application nor in the parent PCT application, and thus, lined-through in their corresponding PTO-1449.

Signed copies of the PTO-1449 are attached hereto.

Drawings

The drawings filed on November 30, 2000 are acceptable.

Claim Objections

Claim 1 is objected to because of the following informalities: MPEP 608.01(m) states that each claim begins with a capital letter and ends with a period and that, "***[p]eriods may not be used elsewhere in the claims except for abbreviations***." Claim 1, however, recites multiple periods after each sub-step of (i) through (vi).

Claim 10 appears to be missing a preposition in the phrase, "monitoring the detectable signal....with a monitoring device in real *time various* stages of electronic hybridization..." It appears that a preposition in the likes of, "during," should be inserted between the *italicized* words.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 2 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 recites the limitation "the target nucleic acid sequence." There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-5, 7-9, 12-14, 16, 17, and 19-21 are rejected under 35 U.S.C. 102(e) as being anticipated by Nerenberg et al. (U.S. Patent No. 6,468,742 B2, issued October 22, 2002, priority February 25, 1998).

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Nerenberg et al. disclose a method of using an electronically addressable array for the purpose of detecting Single Nucleotide Polymorphism (Abstract). The method disclosed by Nerenberg et al. involves the following steps:

a) providing at least one sample nucleic acid containing at least one target nucleic acid (column 16, lines 22-25) on a electronically addressable array;

b) electronically biasing one or more specified test sites (column 6, lines 25-27);

c) immobilizing the target nucleic acid to the test sites by avidin/streptavidin interaction (column 6, lines 25-27; column 16, lines 40-44);

d) electronically hybridizing a first and second probes to the immobilized nucleic acid, wherein the first probe is specific for a wild-type allele and the second probe is specific for a mutant (*i.e.,* polymorphic) allele (column 16, lines 30-36), each labeled with different labels (column 7, line 52-53; column 17, line 60), such as cy3 and cy5 (column 13, line 61);

e) performing electronic stringency on the hybridized complexes (column 6, lines 43-58); and

f) detecting the hybridization complexes (column 16, lines 64-67),

thereby anticipating the method of instant claims 1, 7, 13, and 14.

Nerenberg et al. disclose that the target nucleic acid can be amplified prior to their immobilization (column 16, line 24), thereby anticipating instant claim 2.

At least one wild-type and single nucleotide polymorphism is identified by the method of Nerenberg et al., (therefore, at least bi-allelic) and wherein all possible single polymorphism could be detected (column 20, lines 36-40), thereby anticipating instant claims 3, 4, and 12. The target nucleic acid is also disclosed as being from Mannose Binding protein gene locus that correlates with susceptibility to sepsis in leukopenic patients (column 21, lines 63-66), or in human HLA (or major histocompatibility complex proteins) (column 22, lines 1-6), anticipating instant claim 5.

The method employed by Nerenberg et al. minimizes the mismatches that occur between the target sequence and its hybridization probes (column 6, lines 54-67; column 17, lines 35-40;

Figure 9) to minimize false positives (or reducing the signals from mismatched probes to a background level), thereby anticipating instant claims 8 and 9.

At least two different SNPs (Hemocromatosis locus and Factor V locus) are identified from a sample in the multiplex analysis of target sequences (column 20; Figure 12), thereby anticipating instant claim 16. The method involves an electronic hybridization of the probes for Hemocromatosis, followed by their stripping, further followed by the electronic hybridization of the probes for Factor V (column 20, lines 10-15), anticipating instant claims 19-21.

Additionally, the method of Nerenberg et al. allows the hybridization of the probes and the target nucleic acids prior to the immobilization of the target nucleic acids to the test sites (as evidenced by claims 1 and 2 of Nerenberg et al.), thereby anticipating instant claim 17.

While Nerenberg et al. employ the use of a stabilizer probe to preclude self-complemtarity of the double-stranded target nucleic acid to enhance probe hybridization, the instant claims "comprises" the steps recited therein, allowing for inclusion of other ingredients.

Therefore, Nerenberg et al. anticipate the invention as claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 6 is rejected under 35 U.S.C. 103(a) as being obvious over Nerenberg et al. (U.S. Patent No. 6,468,742 B2, issued October 22, 2002, priority February 25, 1998) in view of Fodor et al. (U.S. Patent No. 6,309,823 B1, issued October 30, 2001, filed January 3, 1997).

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). For applications filed on or after November 29, 1999, this rejection might also be overcome by showing that the subject matter of the reference and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Nerenberg et al. disclose a method of using an electronically addressable array for the purpose of detecting Single Nucleotide Polymorphism (Abstract). The method disclosed by Nerenberg et al. involves the following steps:

a) providing at least one sample nucleic acid containing at least one target nucleic acid (column 16, lines 22-25) on a electronically addressable array;

b) electronically biasing one or more specified test sites (column 6, lines 25-27);

c) immobilizing the target nucleic acid to the test sites by avidin/streptavidin interaction (column 6, lines 25-27; column 16, lines 40-44);

d) electronically hybridizing a first and second probes to the immobilized nucleic acid, wherein the first probe is specific for a wild-type allele and the second probe is specific for a mutant (*i.e.,* polymorphic) allele (column 16, lines 30-36), each labeled with different labels (column 7, line 52-53; column 17, line 60), such as cy3 and cy5 (column 13, line 61);

e) performing electronic stringency on the hybridized complexes (column 6, lines 43-58); and

f) detecting the hybridization complexes (column 16, lines 64-67).

Nerenberg et al. do not disclose a method of employing at least one control target nucleic acid.

Fodor et al. disclose a method of detecting polymorphisms via use of an oligonucleotide arrays, wherein the array contains control probes, for the purpose of gauging the background intensity level (column 10, lines 31-35).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to employ the well known technique of employing control probes on a microarray of Nerenberg et al. for the obvious benefit of accounting for background (or noise

level) prevalent in a hybridization assay. One of ordinary skill in the art would have had a reasonable expectation of success in combining the teachings as the use of control probes in the array hybridization, as demonstrated by Fodor et al., have been well-established in the art.

MPEP, at 2143.02, states that the prior art can be modified or combined to reject claims as obvious as long as there is a reasonable expectation of success. Given that the use of control probes in microarray for the benefit of accounting for background hybridization has been well-established, one of ordinary skill in the art microarray would have had a reasonable expectation of the success at arriving at the claimed invention, rendering the claims obvious over the cited references.

Therefore, for the above reasons, the invention as claimed is *prima facie* obvious over the cited references.

Claims 10, 11, 15, and 18 are rejected under 35 U.S.C. 103(a) as being obvious over Nerenberg et al. (U.S. Patent No. 6,468,742 B2, issued October 22, 2002, priority February 25, 1998) in view of Heller et al. (U.S. Patent No. 6,048,690, issued April 11, 2000, filed May 14, 1997).

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference

under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). For applications filed on or after November 29, 1999, this rejection might also be overcome by showing that the subject matter of the reference and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Nerenberg et al. disclose a method of using an electronically addressable array for the purpose of detecting Single Nucleotide Polymorphism (Abstract). The method disclosed by Nerenberg et al. involves the following steps:

a) providing at least one sample nucleic acid containing at least one target nucleic acid (column 16, lines 22-25) on a electronically addressable array;

b) electronically biasing one or more specified test sites (column 6, lines 25-27);

c) immobilizing the target nucleic acid to the test sites by avidin/streptavidin interaction (column 6, lines 25-27; column 16, lines 40-44);

d) electronically hybridizing a first and second differently labeled probes to the immobilized nucleic acid, wherein the first probe is specific for a wild-type allele and the second probe is specific for a mutant (*i.e.,* polymorphic) allele (column 16, lines 30-36), each labeled with different labels (column 7, line 52-53; column 17, line 60), such as cy3 and cy5 (column 13, line 61);

e) performing electronic stringency on the hybridized complexes (column 6, lines 43-58); and

f) detecting the hybridization complexes (column 16, lines 64-67)

The method employed by Nerenberg et al. minimizes the mismatches that occur between the target sequence and its hybridization probes (column 6, lines 54-67; column 17, lines 35-40; Figure 9) to minimize false positives (or reducing the signals from mismatched probes to a background level), (meeting instant claims 8).

The method of Nerenberg et al. allows the hybridization of the probes and the target nucleic acids prior to the immobilization of the target nucleic acids to the test sites (as evidenced by claims 1 and 2 of Nerenberg et al.), (instant claim 17).

Nerenberg et al. do not explicitly disclose the method which monitors the detectable signal from hybridization complexes between the target nucleic acid and the labeled probes, in real time during various stages of electronic hybridization and stringency in order to determine the melting point of the probes and target nucleic acid sequence (instant claim 10), wherein the power level or length of time of the electronic stringency is controlled based on the signal detection (instant claim 11).

Nerenberg et al. do not explicitly disclose that the plurality of sample nucleic acids from each patient samples are immobilized on one test site, wherein each sample nucleic acid of each patient sample comprises a different SNP locus (instant claim 15).

Nerenberg et al. do not explicitly disclose that the patient sample nucleic acids, after their hybridization to their probes, are sequentially immobilized onto the test sites (instant claim 18).

Heller et al. disclose a method of employing the same electronically addressable array of Nerenberg et al. for the purpose of determining the FPE, or fluorescent perturbation effect, which is a powerful analytical tool for efficient discrimination of match/mismatch DNA hybrids (column 5, lines 15-20). The method involves the monitoring of the relative fluorescent intensity of the hybridized probes with respect to the voltage applied (Figure 1A and 1B, therefore meets instant claims 10 and 11).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Nerenberg et al. with that of Heller et al. to arrive at the claimed invention for the following reasons.

Nerenberg et al. recgonizes the importance of being able to distinguish between the match and mismatched probes, wherein the artisans state:

"Moreoever, electronic biasing equally facilitates distinguishing hybridization mismatches occurring at the terminal nucleic acid pairs of a hybridized duplex as well as destabilizing mismatches occurring internally...allow[ing] the current invention to be less restricted in choices for positioning the location of SNP bases on probes..." (column 6, lines 54-61).

Heller et al. disclose that the fluorescent signal from labeled probes or target DNAs was perturbed during the initiation of electronic dehybridization (or stringency) ***at or around the electronic power levels (current and voltage)*** resulting as a, "rise or spike in the fluorescence intensity prior to dehybridization of the fluorescent labeled probe sequence from the DNA sequence attached to the microscopic test site (column 10, lines 40-49), allowing the

match/mismatch discrimination of the probes to be carried out, "***very rapidly***...compared to classical hybridization stringency process...." (column 11, lines 1-5).

Therefore, one of ordinary skill in the art would have been motivated to adopt the teachings of Heller et al., who employ the same electronically addressable array as Nerenberg et al. to arrive at the method of determining the FPE, for the advantage of efficiently discriminating the match and mismatch of probes-target duplex (*i.e.,* further improving the mismatch discrimination already recognized by Nerenberg et al.) with a reasonable expectation of success.

With regard to whether the plurality of sample nucleic acids from each patient samples are immobilized on one test site or different test sites, and whether each sample nucleic acid of from each patient sample comprises a different SNP locus, such is an obvious design modification that is considered to be well within the purview of an ordinarily skilled artisan in the array design (*i.e.,* Affymetrix™).

Finally, with regard to the patient sample nucleic acids, after their hybridization to their probes, being sequentially immobilized onto the test sites, as all nucleic acids must first be immobilized on to the test sites prior to their detection, one of ordinary skill in the art would have recognized that the probe-target hybridization duplex, had to be sequentially immobilized on to their test site for the subsequent detection method with a reasonable expectation of success.

In *In re Preda*, 401 F.2d 825, 826, 159 USPQ 342 (CCPA 1968), the court expressed that, "in considering the disclosure of a reference, it is proper to take into account not only specific teachings of the reference but also the inference which one skilled in the art would reasonably be expected to draw therefrom."

Therefore, for the above reasons, the claims are *prima facie* obvious over the cited references.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-5, 7-9, 12-14, 16, 17, and 19-21 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 12, 14, 16, 22, 32, and 33 of U.S. Patent No. 6,468,742 B2 (hereto referred to as '742 patent). Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons:

Claims of the instant application is broadly drawn to a method of detecting a single nucleotide polymorphism involving the use of a microelectronic chip, utilizing electronic stringency controls.

Claim 1 of the '742 patent is drawn to a method for determining the presence of a specific sequence in at least one genetic locus of one or more target nucleic acids of interest in at least one sample of interest using an electronically addressable capture sites with associated electrodes, the method comprising the following recited steps:

a) contacting a single stranded target nucleic acid of interest with at least one stabilizer oligonucleotide, said stabilizer oligonucleotide hybridizing to or adjacent to a region of expected variance in the target nucleic acid;

b) contacting the target nucleic acid of interest with at least one reporter oligonucleotide, comprising a sequence complementary to at least a portion of the target nucleic acid of interest;

c) electronically addressing the target nucleic acid to at least one capture site on the bioelectronic microchip, wherein the target nucleic acid is captured at the capture site by a capturing means;

d) after (a), (b), and (c), subjecting the hybridized complex to destabilizing conditions;

e) detecting the hybridization of the reporters oligonucleotide to the target nucleic acid.

Claim 2 of the '742 patent then recites that step (c) is conducted prior to steps (a) and (b), which results in the instant claim 1. While the claims do not explicitly state that the variance is a polymorphism, the specification of '742 is drawn to the method of identifying SNPs (as already discussed above), rendering instant claims 1 and 12 obvious.

Claim 22 of the '742 patent recites the obvious step of amplifying the target nucleic acids, meeting the limitation of instant claim 2.

With regard to the SNP locus being bi-allelic or multi-allelic as in instant claims 3 and 4, such is obvious in view of the disclosure on column 20, lines 36-40 of the '742 patent, which allows the identification of at least one wild-type and single nucleotide polymorphism or all possible single polymorphism.

With regard to the method being directed to detecting SNPs from nucleic acid of instant claim 5, such is obvious in view of the disclosed nucleic acid species – Mannose Binding protein

gene locus that correlates with susceptibility to sepsis in leukopenic patients (column 21, lines 63-66), or in human HLA (or major histocompatibility complex proteins) disclosed in column 22, lines 1-6 of the '742 patent.

With regard instant claim 7, claim 12 of the '742 patent recites that the sample nucleic acid comprising a biotin moiety is immobilized on the capture site of the array based on biotin-binding moiety present at a capture site, wherein said interaction is disclosed as being biotin-streptavidin interaction in column 16, lines 40-44 of the '742 patent, rendering instant claim obvious.

With regard to instant claims 8 and 9, such steps are obvious in view of column 6, lines 54-67; column 17, lines 35-40; and Figure 9 of the instant specification which demonstrates the well-known technique of minimizing the mismatches that occur between the target sequence and its hybridization probes in order to minimize false positives (or reducing the signals from mismatched probes to a background level).

With regard to instant claims 13-14, and 16 drawn to the first and second probe being differently labeled, and the labels being Cy3 and Cy5, and the detection of different SNPs in target nucleic acid, claims 14, 16, 32, and 33 of the '742 patent, as well as on column 20 and Figure 12 of its specification discloses that at least two different SNPs (Hemocromatosis locus and Factor V locus) are identified from a sample in the multiplex analysis of target sequences.

Additionally, the method of Nerenberg et al. allows the hybridization of the probes to the target nucleic acids occur prior to the immobilization of the target nucleic acids to the test sites (as evidenced by claims 1 and 2 of Nerenberg et al.), thereby meeting instant claim 17.

With regard instant claims 19-21, drawn to repeating the SNP detection with at least one additional mixture of first and second probes, method involving stripping of the first-applied first and second probes, claim 17 of the '742 patent recites that at least one specific sequence in at least one genetic loci is "sequentially" performed, wherein the specification of the '742 patent gives such example as involving an electronic hybridization of the probes for Hemocromatosis, followed by their stripping, then followed by the electronic hybridization of the probes for Factor V (column 20, lines 10-15).

Since all of the method steps of the instant application, broadly drawn to a genus of using an electronically addressable array for the detection of SNPs in a target nucleic acid are disclosed by the claims of the '742 patent, claims are rendered obvious for the above reasons.

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claims are not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would be obvious over, the reference claim(s). see, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

Claim 6 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 2 of U.S. Patent No. 6,468,742 B2 (hereto referred to as '742 patent in view of Fodor et al. (U.S. Patent No. 6,309,823 B1, issued October 30, 2001, filed January 3, 1997).

Claims of the instant application is broadly drawn to a method of detecting a single nucleotide polymorphism involving the use of a microelectronic chip, utilizing electronic stringency controls.

Claim 1 of the '742 patent is drawn to a method for determining the presence of a specific sequence in at least one genetic locus of one or more target nucleic acids of interest in at least one sample of interest using an electronically addressable capture sites with associated electrodes, the method comprising the following recited steps:

a) contacting a single stranded target nucleic acid of interest with at least one stabilizer oligonucleotide, said stabilizer oligonucleotide hybridizing to or adjacent to a region of expected variance in the target nucleic acid;

b) contacting the target nucleic acid of interest with at least one reporter oligonucleotide, comprising a sequence complementary to at least a portion of the target nucleic acid of interest;

c) electronically addressing the target nucleic acid to at least one capture site on the bioelectronic microchip, wherein the target nucleic acid is captured at the capture site by a capturing means;

d) after (a), (b), and (c), subjecting the hybridized complex to destabilizing conditions;

e) detecting the hybridization of the reporters oligonucleotide to the target nucleic acid.

Claim 2 of the '742 patent then recites that step (c) is conducted prior to steps (a) and (b), which results in the instant claim 1. While the claims do not explicitly state that the variance is a polymorphism, the specification of '742 is drawn to the method of identifying SNPs (as already discussed above).

Nerenberg et al. do not disclose a method of employing at least one control target nucleic acid.

Fodor et al. disclose a method of detecting polymorphisms via use of an oligonucleotide arrays, wherein the array contains control probes, for the purpose of gauging the background intensity level (column 10, lines 31-35).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to employ the well known technique of employing control probes on a microarray of Nerenberg et al. for the obvious benefit of accounting for background (or noise level) prevalent in a hybridization assay. One of ordinary skill in the art would have had a reasonable expectation of success in combining the teachings as the use of control probes in the array hybridization, as demonstrated by Fodor et al., have been well-established in the art.

MPEP, at 2143.02, states that the prior art can be modified or combined to reject claims as obvious as long as there is a reasonable expectation of success. Given that the use of control probes in microarray for the benefit of accounting for background hybridization has been well-established, one of ordinary skill in the art microarray would have had a reasonable expectation of the success in making design modification to achieve the same method with a reasonable expectation of success, rendering the claims obvious over the cited references.
Therefore, for the above reasons, the invention as claimed is *prima facie* obvious over the cited references.

Claims 10, 11, 15, and 18 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 2 of U.S. Patent No.

6,468,742 B2 (hereto referred to as '742 patent) in view of Heller et al. (U.S. Patent No. 6,048,690, issued April 11, 2000, filed May 14, 1997).

Teachings of the '742 Patent have been already discussed above.

The '742 patent do not explicitly disclose the method which monitors the detectable signal from hybridization complexes between the target nucleic acid and the labeled probes, in real time during various stages of electronic hybridization and stringency in order to determine the melting point of the probes and target nucleic acid sequence (instant claim 10), wherein the power level or length of time of the electronic stringency is controlled based on the signal detection (instant claim 11).

The '742 patent do not explicitly disclose that the plurality of sample nucleic acids from each patient samples are immobilized on one test site, wherein each sample nucleic acid of each patient sample comprises a different SNP locus (instant claim 15).

The '742 patent do not explicitly disclose that the patient sample nucleic acids, after their hybridization to their probes, are sequentially immobilized onto the test sites (instant claim 18).

Heller et al. disclose a method of employing the same electronically addressable array of the '742 patent for the purpose of determining the FPE, or fluorescent perturbation effect, which is a powerful analytical tool for efficient discrimination of match/mismatch DNA hybrids (column 5, lines 15-20). The method involves the monitoring of the relative fluorescent intensity of the hybridized probes with respect to the voltage applied (Figure 1A and 1B, therefore meets instant claims 10 and 11).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of the '742 patent with that of Heller et al. to arrive at the claimed invention for the following reasons.

Nerenberg et al. recgonizes the importance of being able to distinguish between the match and mismatched probes, wherein the artisans state:

"Moreoever, electronic biasing equally facilitates distinguishing hybridization mismatches occurring at the terminal nucleic acid pairs of a hybridized duplex as well as destabilizing mismatches occurring internally...allow[ing] the current invention to be less restricted in choices for positioning the location of SNP bases on probes..." (column 6, lines 54-61).

Heller et al. disclose that the fluorescent signal from labeled probes or target DNAs was perturbed during the initiation of electronic dehybridization (or stringency) ***at or around the electronic power levels (current and voltage)*** resulting as a, "rise or spike in the fluorescence intensity prior to dehybridization of the fluorescent labeled probe sequence from the DNA sequence attached to the microscopic test site (column 10, lines 40-49), allowing the match/mismatch discrimination of the probes to be carried out, "***very rapidly***...compared to classical hybridization stringency process...." (column 11, lines 1-5).

Therefore, one of ordinary skill in the art would have been motivated to adopt the teachings of Heller et al., who employ the same electronically addressable array as Nerenberg et al. to arrive at the method of determining the FPE, for the advantage of efficiently discriminating the match and mismatch of probes-target duplex (*i.e.,* further improving the mismatch discrimination already recognized by Nerenberg et al.) with a reasonable expectation of success.

With regard to whether the plurality of sample nucleic acids from each patient samples are immobilized on one test site or different test sites, and whether each sample nucleic acid of from each patient sample comprises a different SNP locus, such is an obvious design modification that is considered to be well within the purview of an ordinarily skilled artisan in the array design (*i.e.,* Affymetrix™).

Finally, with regard to the patient sample nucleic acids, after their hybridization to their probes, being sequentially immobilized onto the test sites, as all nucleic acids must first be immobilized on to the test sites prior to their detection, one of ordinary skill in the art would have recognized that the probe-target hybridization duplex, had to be sequentially immobilized on to their test site for the subsequent detection method with a reasonable expectation of success.

In *In re Preda*, 401 F.2d 825, 826, 159 USPQ 342 (CCPA 1968), the court expressed that, "in considering the disclosure of a reference, it is proper to take into account not only specific teachings of the reference but also the inference which one skilled in the art would reasonably be expected to draw therefrom."

Therefore, for the above reasons, the claims are *prima facie* obvious over the cited references.

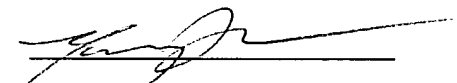
Conclusion

No claims are allowed.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (571) 272-0785. The Examiner can normally be reached from 8:30 a.m. to 6:00 p.m. Monday through Thursday. If attempts to reach the Examiner by telephone are unsuccessful, the Primary Examiner in charge

of the prosecution, Dr. Kenneth Horlick, can be reached at (571) 272-0784. If the attempts to reach the above Examiners are unsuccessful, the Examiner's supervisor, Gary Benzion, can be reached at (571) 272-0782. Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. All official documents must be sent to the Official Tech Center Fax number: (703) 872-9306. For Unofficial documents, faxes can be sent directly to the Examiner at (517) 273-0785. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-0507.



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5/1/04